REMARKS

Introduction

This paper is submitted in response to the March 31, 2005 Office Action for the above-identified patent application. Claims 42-51, 53, 55, 56, 82, 85 and 86 are pending and have been rejected. Claims 87-92 have been newly added.

Applicants thank the Examiner for withdrawing the previous objections and rejections under 35 U.S.C. §101, §112, 1st and 2nd paragraphs, and the obviousness-type double patenting rejection.

Amendments to the Claims

Applicants have amended claims 43-45 to depend from claim 47 or 87.

Applicants have amended claims 48-53, 82 and 85 to recite a "host cell." Applicants have further amended claim 48 to recite "wherein the polypeptide is produced from the nucleic acid." Support for the amendments is found throughout the specification, *e.g.*, on page 6, lines 25-30; page 7, lines 1-14 and line 28 to page 8, line 21, page 18, lines 1-27; page 19, lines 14-19, and page 26, line 29 to page 28, line 29.

Applicants have amended claims 49-51 to depend from claim 48 or 88. Applicants have further amended claims 49 and 53 to delete reference to an "insoluble" polypeptide. Support for the amendments is found throughout the specification, *e.g.*, on page 6, lines 25-30; page 7, lines 1-14 and line 28 to page 8, line 21.

Applicants have further amended claim 53 to recite "wherein the polypeptide is produced from the nucleic acid." Support for the amendments is found throughout the

specification, *e.g.*, on page 6, lines 25-30; page 7, lines 1-14, and line 28 to page 8, line 21, and page 24, line 9 to page 44, line 5.

Applicants have amended claim 55 to depend from "claim 42 or 87" and to recite that "said nucleic acid has an overall AT content of less than 70%." Applicants have further amended claim 56 to recite that "said nucleic acid has an overall AT content of less than about 60%." Support for the amendments is found, *e.g.*, on page 14, lines 16-28 of the specification as filed.

Applicants have amended claim 85 to recite "wherein the host cell expresses the nucleic acid and wherein a polypeptide having the amino acid sequence of SEQ ID NO:4 is expressed." Support for the amendment is found throughout the specification, *e.g.*, on page 6, lines 25-30; page 7, lines 1-14, and line 28 to page 8, line 21, and page 24, line 9 to page 44, line 5.

Applicants have added claim 87, drawn to an isolated nucleic acid comprising the nucleic acid sequence of SEQ ID NO:3. Support for the added claim is found *e.g.*, on page 15, lines 1-12 and in Figure 2 of the specification.

Applicants have added claims 88-90, drawn to methods of preparing a polypeptide. Support for the added claims is found, *e.g.*, on page 6, lines 25-30; page 7, lines 1-14 and 28 to page 8, line 21; page 19, lines 14-19; and page 26, line 29 to page 28, line 29 of the specification.

Applicants have added claims 91-92, drawn to methods of isolating an immunogenic polypeptide. Support for the added claims is found, *e.g.*, on page 6, lines 25-30;

page 7, lines 1-14 and line 28 to page 8, line 21; page 10, line 29 to page 11, line 17; and page 24, line 9 to page 44, line 5 of the specification.

Applicants respectfully request entry of the amendments, which introduce no new matter.

The Objections

The Examiner has objected to claims 50-51 because the recitation of the term "organism" in claims 50-51 allegedly does not further limit claim 48. Applicants have amended claim 50 to recite that the "host cell" is *Escherichia coli*. Applicants have amended claim 51 to recite that the "yeast" is *Pichia pastoris*.

The Examiner has objected to claims 55-56 because of the recitation of "claim claim 42." Applicants note that only claim 55 has the duplicated term. Accordingly, applicants have amended claim 55 to remove the duplicated "claim."

The Rejections Under 35 U.S.C. §112, 2¶ Should Be Withdrawn

The Examiner has rejected claims 42-51, 53, 55, 56, 82, 85 and 86 under 35 U.S.C. §112, 2nd paragraph for failing to point out and distinctly claim the subject matter that applicant regards as the invention.

The Examiner has rejected claim 49, alleging that limitation "recovering from said transfected cell at least one insoluble polypeptide" lacks antecedent basis in claim 48, from which it depends, and that the nucleic acid of claim 48 need only be expressed, not translated

into a protein. Applicants have amended claim 48 to recite that the polypeptide is produced from the nucleic acid. As amended, claim 49 distinctly claims the subject matter applicants view as the invention, in compliance with the requirements of 35 U.S.C. §112, 2nd paragraph. Accordingly, applicants request that the rejection be withdrawn.

The Examiner has rejected claims 50-51 because the phrase "wherein said organism" lacks antecedent basis in claim 48, from which claims 50-51 depend. Applicants have amended claim 48 to recite "transfecting a host cell." Applicants have also amended claims 50 and 51 to recite "host cell." In view of the amendments, applicants submit that claims 50 and 51 distinctly claim the subject matter applicants view as the invention, in compliance with the requirements of 35 U.S.C. §112, 2nd paragraph, and request that the rejections be withdrawn.

The Examiner has rejected claim 53 because the phrase "insoluble polypeptide" lacks antecedent basis. Applicants have amended claim 53 to recite that the polypeptide is produced from said nucleic acid and to delete the term "insoluble." As amended, applicants submit that claim 53 complies with the requirements of 35 U.S.C. §112, 2nd paragraph and request that the rejection be withdrawn.

The Examiner has rejected claims 55-56 allegedly because the claim limitation "the AT content" lacks antecedent basis in claim 42, from which claims 55-56 depend. Applicants have amended claim 55 to recite that "the nucleic acid has an overall AT content of." Accordingly, applicants request that the rejection of claims 55-56 be withdrawn.

The Examiner has rejected claims 85-86 allegedly because the limitations "said polypeptide is at least 0.75% (w/v) of the total cellular protein" or "said polypeptide is at least 20% (w/v) of the total cellular protein," respectively, lack antecedent basis in claims 82, 45 and

42, from which claims 85-86 depend. In view of applicants' amendment to claim 85, applicants assert that the claims 85-86 are definite and comply with the requirements of 35 U.S.C. §112, 2nd paragraph, and request that the rejection of claims 55-56 be withdrawn.

The Rejections Under 35 U.S.C. §102(b) Should Be Withdrawn

Kuruazono *et a*l. Does Not Anticipate the Claimed Subject Matter

The Examiner has rejected claims 42-47, 55 and 82 under 35 U.S.C. §102(b) as allegedly being anticipated by Kurazono *et al.* (hereinafter "Kurazono") as evidenced by Dertzbaugh *et al.* ("Mapping of protective and cross-reactive domains of the type A neurotoxin of Clostridium botulinum," *Vaccine*, 14, 1538, 1996) and Binz *et al.* Swiss Prot Accession No. P10845 (hereinafter "Binz"). The Examiner alleges that Kurazono teaches (1) an isolated or purified nucleic acid fragment of botulinum neurotoxin serotype A, (2) the amino acid comprising at least one epitope of SEQ ID NO:4; (3) an expression vector comprising a nucleic acid encoding at least one epitope of SEQ ID NO:4.; (4) a nucleic acid wherein the AT content is less than about 70% of the total base composition; and (5) a recombinant host cell comprising a nucleic acid of claim 45. Applicants traverse.

Kurazono used Binz's nucleic acid sequence (identified both as Genbank Accession No. M30196 and GI 144864), which encodes the amino acid sequence of Swiss Prot Accession No. P10845, which is the amino acid sequence of a wild-type botulinum neurotoxin serotype A heavy chain. The amino acid sequence of SEQ ID NO:4 of the instant invention is not the same as the amino acid sequence of P10845. Applicants invite the Examiner's attention

to a sequence alignment of the two sequences, attached hereto at Exhibit A. Applicant's SEQ ID NO:4 ("SEQ") differs from P1085 at position 1 (SEQ) and position 863 (P10845). Moreover, Binz's nucleic acid sequence M30196/144864 is not the same sequence as the nucleic acid sequence of SEQ ID NO:3 of the instant invention. Applicants invite the Examiner's attention to a sequence alignment of M30196/144864 and SEQ ID NO:3, attached hereto at Exhibit B. In the sequence alignment, "Sequence 1," ("Query") is nucleic acid sequence 144864; "Sequence 2," ("Sbjct") is SEQ ID NO:3. In the alignment, identical nucleotides are indicated by a bar between the aligned sequences. Thus, in view of the amendments to the claims and because Kurazono does not teach or suggest the claimed subject matter, applicants respectfully request that the rejection under 35 U.S.C. §102(b) be withdrawn.

LaPenotiere *et al.* and Thompson *et al.* Do Not Anticipate the Claimed Subject Matter

The Examiner has rejected claims 42-50, 53, 55 and 82 under 35 U.S.C. §102(b) as allegedly being anticipated by LaPenotiere *et a*l. ("Development of molecular engineered vaccine for *C. Botulinum* neurotoxins," in *Botulinum and Tetanus Neurotoxins*, Plenum Press, NY, 1993) (hereinafter "LaPenotiere"). The Examiner alleges that LaPenotiere discloses a (1) nucleic acid of botulinum neurotoxin serotype A Hc fragment, which, when expressed, induces a protective immune response; (2) an expression vector comprising the nucleic acid; (3) a host cell comprising the expression vector, and (4) a method of preparing a polypeptide comprising transfecting a cell with the nucleic acid having at least one immunogenic epitope of SEQ ID NO:4, culturing the transfected cells wherein the nucleic acid is expressed and recovering the insoluble polypeptide.

The Examiner has also rejected claims 42-45, 28, 50, 55 and 80 as allegedly anticipated by Thompson *et al.* ("The complete amino acid sequence of the *Clostridium botulinum* type A neurotoxin, deduced by nucleotide analysis of the encoding gene," *Eur. J. Biochem*, 7, 1043, 1990) (hereinafter "Thompson"). The Examiner alleges that Thompson discloses (1) an isolated and purified nucleic acid comprising at least one immunogenic epitope encoded by SEQ ID NO:4 and a nucleic acid sequence of SEQ ID NO:3; (2) an expression vector comprising the nucleic acid; (3) a nucleic acid comprising less than about 70% d(A/T) content; (3) a recombinant host comprising the nucleic acid sequence; and (4) methods of preparing a polypeptide, comprising transfecting a cell with a nucleic acid encoding a polypeptide comprising an amino acid sequence that is at least one epitope of SEQ ID NO:4, and culturing the cell under conditions wherein the nucleic acid is expressed. Applicants traverse.

Both LaPenotiere and Thompson teach a nucleic acid sequence of a wild-type botulinum neurotoxin serotype A heavy chain. Moreover, both LaPenotiere and Thompson utilized the same nucleic acid sequence that encodes a wild-type portion of the carboxy terminus of a botulinum neurotoxin type A heavy chain. In fact, LaPenotiere teaches that the nucleic acid sequence used therein was isolated from plasmid pCDA3 ("The DNA clone coding for the H_c domain of *C. botulinum* toxin serotype A was pCBA3, kindly provided by Nigel Minton."). *See* LaPenotiere, page 464, lines 15-16 (citing Thompson *et al.*, *Eur. J. Biochem.*, 189, 73, 1990). Thompson's nucleic acid sequence, identified as both Genbank Accession No. X52066 and GI 40381, encodes an amino acid sequence that is also identified as P10845. *See* Exhibit C, page 3, highlighted in yellow. As shown by the alignment at Exhibit A, the amino acid sequence of SEQ ID NO:4 and the amino acid sequence of P10845 are not the same.

Moreover, the nucleic acid sequence of SEQ ID NO:3 is not the same as the nucleic acid sequence of X50266. Applicants invite the Examiner's attention to a sequence alignment of the two sequences, attached hereto at Exhibit D. In the sequence alignment, Sequence 1 ("Query") is Thompson's nucleic acid sequence, GI 40381; Sequence 2 ("Sbjct") is SEQ ID NO:3 of the instant invention. As shown in the alignment, identical nucleotides are indicated by a bar between the aligned sequences. Thus, in view of the amendments to the claims and because LaPenotiere and Thompson do not teach the subject matter of claims 42-50, 53, 55 and 82 and claims 42-45, 48, 50, 55 and 82, respectively, applicants respectfully request that the rejection under 35 U.S.C. §102(b) be withdrawn.

Conclusion

Applicants believe that the application is in condition for allowance and respectfully request favorable action. The Examiner is kindly invited to contact the undersigned if helpful to advance the application to allowance.

A one (1) month extension to the time for responding to the Office Action is respectfully requested and the appropriate fee is enclosed. Applicants believe that no additional fees are due. In the event that fees are due, however, the Director is hereby authorized to charge payment of any such fees to Deposit Account No. 02-4377.

Respectfully submitted,

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